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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/540,963	03/31/00	KUPPER T	B0801/777170

HM12/1004

WOLF GREENFIELD & SACKS P C
600 ATLANTIC AVENUE
BOSTON MA 02210

EXAMINER	
BECKERLEG,A	
ART UNIT	**PAPER NUMBER**
1632	7

DATE MAILED: 10/04/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/540,963	KUPPER ET AL.	
	Examiner	Art Unit	
	Anne M Beckerleg	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,5-7,12,13,18-21,25,28-30,36,37 and 48 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,5-7,12,13,18-21,25,28-30,36,37 and 48 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-7, 12-14, 18-21, 25, 28-30, 36-37, and 48 are rejected under 35 U.S.C. 112, first paragraph rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the following: 1) methods of delivering recombinant dendritic cells which express a melanoma tumor specific antigen to peripheral lymph nodes in vivo comprising further transfecting said cells with an expression vector encoding a chimeric E/L selectin polypeptide and administering said cells to a mammal wherein the expression of the chimeric E/L selectin is capable of homing the transfected cells to peripheral lymph nodes in vivo, and 2) methods of inhibiting the growth of a melanoma in a subject comprising administering recombinant dendritic cells with express a melanoma tumor specific antigen and have been transfected with a expression vector encoding a chimeric E/L selectin polypeptide, wherein the expression of the chimeric E/L selectin is capable of homing the transfected cells to peripheral lymph nodes in vivo and inhibiting the growth of a melanoma which expresses the same melanoma specific tumor antigen expressed by the recombinant dendritic cells, does not reasonable provide enablement for methods of

delivering recombinant dendritic cells to any tissue in a mammal by transfecting said cell with any portion of an L, E, or P selectin, methods of delivering recombinant dendritic cells to any tissue in a mammal administering compositions comprising activated platelets and dendritic cells, or methods of vaccinating against any disease comprising administering the dendritic cells and dendritic cell compositions disclosed by the specification. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. It is further noted that the specification does not teach any purpose for directing the dendritic cells to tissues or secondary lymph nodes other than for the vaccination against disease, particularly cancer.

The specification fails to provide an enabling disclosure for targeting dendritic cells to any type of tissue, lymphoid or otherwise, comprising genetically modifying dendritic cells to express a portion of L-selectin, E-selectin, or P-selectin. The specification further does not provide sufficient enablement for targeting any dendritic cell to any particular type of tissue in vivo comprising administering a combination of activated platelets and dendritic cells. The specification discloses that dendritic cells are potent antigen presenting cells and speculates that homing dendritic cells to peripheral lymph nodes or sites of chronic inflammation will have result in an increased therapeutic effect on various pathogenic infections and cancer. The specification teaches that dendritic cells cultured in vitro fail to home to peripheral lymph nodes and theorizes that the inability of dendritic cells to accumulate in peripheral lymph nodes is due to the low level of L-selectin on the dendritic cells. The specification further teaches that L-selectin is the main selectin

responsible for lymphocyte homing to peripheral lymph nodes in vivo via binding with peripheral node addressins (PNAds). However, the specification's working examples clearly demonstrate that the transduction of dendritic cells with an retrovirus encoding L-selectin did not result in expression of L-selectin on the dendritic cell surface (specification, page 28, lines 1-4). The specification explains that L-selectin may have been rapidly degraded from the dendritic cell surface and therefore teaches the use of an E/L-selectin chimera which contains the transmembrane and intracellular domains of L-selectin and the extracellular domain of E-selectin. The specification's working examples demonstrate that dendritic cells transduced with the E/L-selectin express the E/L-selectin chimera and are capable of tethering and rolling both in vitro and in vivo on PNAd. Therefore, based on the applicant's own data, the skilled artisan would not have predicted that dendritic cells could be transfected to express sufficient levels of L-selectin capable of directing the transfected dendritic cells to peripheral lymph nodes or any other tissues in vivo. Further, the specification fails to provide any guidance concerning the ability of E-selection or P-selectin to target dendritic cells to lymph nodes or any other tissue in vivo. E-selectin is primarily expressed by endothelial cells, whereas P-selectin is primarily expressed by platelets. Receptors for E-selectin and P-selectin are present on a number of cells which are present in many different cellular locations and are not limited to peripheral lymph nodes. P-selectin for example naturally serves as a adhesion molecule for leukocytes. While E-selectin and P-selectin may have the potential to bind to elements of PNAds, the specification fails to teach the level of E-selectin or P-selectin expression on dendritic cells sufficient to result in accumulation of dendritic cells in

peripheral lymph nodes. At the time of filing, the art teaches that the process of tethering and rolling mediated by selectins is affected by the density of the selectin on the rolling cell, the identity of the selectin, the location of selectin expression on the cell surface, e.g. dispersed versus localized to the microvillus, and the density of receptors on the target cell surface (Stein et al. (1999) J. Exp. Med., Vol. 189 (1), 37-49, see pages 47-48). The specification fails to provide sufficient guidance for these parameters in regards to the any selectin other than the disclosed E/L-selectin. Further, as stated above, based on the expression of E-selectin and P-selectin ligands on cells located outside peripheral lymph nodes, the skilled artisan would not have predicted that the expression of either E-selectin or P-selectin would in fact target transfected dendritic cells solely to the peripheral lymph node. In regards to the targeting of non-lymphoid tissue, the specification fails to teach the level of expression of any full length or chimeric selectin capable of specifically targeting any non-lymphoid tissue. Thus, based on the nature or tethering and rolling mediated by selectins, the expression patterns of selectin ligands in vivo, the lack of guidance provided by the specification for the parameters affecting the targeting of specific cells to peripheral lymph nodes versus other tissues in vivo using selectin mediated adhesion, the specification's own data demonstrating the lack of expression of L-selectin in dendritic cells transduced with L-selectin, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to practice the scope of the invention as claimed, and the skilled artisan would not have been able to predict whether the expression of any ligand binding portion of a selectin on a dendritic cell would target that cell to any particular tissue in vivo.

The specification does not provide any guidance as to the amount of dendritic cells accumulating at a particular tissue in a mammal necessary to induce any type of immune response in the mammal. The specification further fails to teach the level and character of any immune response, either antigen specific or non-specific, which correlates with any therapeutic effect on any pathogenic infection or disease. While the specification's working examples demonstrate the ability of dendritic cells transduced with the E/L-selectin and dendritic cell/activated platelet complexes to bind to PNAds in peripheral lymph nodes, the specification fails to correlate the level of dendritic cell binding with the generation of any type of immune response or with the treatment or prevention of any type of pathogenic infection or disease. As noted above, the specification clearly teaches that purpose of directing dendritic cells to peripheral lymph nodes or sites of chronic inflammation is for the vaccination or treatment of infection or disease, in particular cancer. While dendritic pulsed with antigen or genetically modified to express a particular antigen have been demonstrated in the art to be capable of eliciting antigen specific immune responses against viral and tumor specific antigens, naive dendritic cells have not been demonstrated to be capable of generating any specific types of immune responses or to be capable of having any therapeutic effect on any disease. In order to generate a therapeutic immune response, it is necessary for naive lymphocytes to be activated by professional antigen presenting cells which present a immunogenic peptide epitope. In the absence of an immunogen, the lymphocytes are not activated. The specification provides not evidence that naive dendritic cells directed against any tissue in a mammal including the peripheral lymph nodes would be capable of

activating any lymphocytes or generating any type of immune response capable of having a therapeutic effect on any disease. Based on the nature of dendritic cell induction of immune responses, which requires the presentation of immunogenic antigen, and in the absence of evidence to the contrary, the skilled artisan would not have predicted that the administration of naive dendritic cells would result in any therapeutic effect on any disease.

It is further noted that at the time of filing, the targeting of vectors or cells to specific tissues or cells types in vivo was considered highly unpredictable. Deonarain, in a review entitled, " Ligand-targeted receptor-mediated vectors for gene delivery", teaches that one of the main obstacles to successful gene therapy is, " ... the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time", and states that, " .. even after almost 30 years of relentless pursuit, nothing has yet delivered such a promise in terms of clinical results" (Deonarain et al. (1998) Exp. Opin. Ther. Patents, Vol. 8 (1), page 53, lines 1-4, and page 54, lines 12-15). Miller et al. concurs, teaching that the development of surface targeting has been problematic and that the biggest challenge in targeted vector design is to combine targeting with efficiency of gene expression, since , " attainment of one usually compromises the other" (Miller et al. (1995) FASEB, Vol. 9, page 198, paragraph 2). As discussed above, the specification fails to provide guidance in the form of detailed teachings or specific working examples for methods to target any dendritic cell to any type of lymphoid or non-lymphoid tissue by expressing any endothelial ligand binding portion of a selectin.

The art at the time of filing further teaches the unpredictability of treating any disease or condition, particularly cancer, using ex vivo immunotherapy. Ross et al. relates that while, " there is only 1 patient to date who might be considered to have had a significant systemic clinical response " to cytokine therapy of a melanoma, "success in a single patient does not imply the general utility of this approach" (Ross et al. (1996) Human Gene Therapy, Vol. 7, page 1786, column 1, paragraph 4). Orkin et al. concurs, stating in regards to the immunotherapy of cancer that, " although several of these strategies show promise in mouse models, none has demonstrated efficacy in humans", and that, " [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol.." (Orkin et al. (1995) page 1, paragraph 3, page 6, paragraph 6). Therefore, based on the art recognized unpredictability of targeting cells in vivo to specific tissues cells, the art recognized unpredictability of treating disease using ex vivo gene therapy, the lack of guidance provided by the specification concerning the parameters affecting dendritic cell targeting to particular tissues using selectins, the lack of correlation between applicant's working examples and the generation of any therapeutic immune response or effect on any disease, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 6-7, 28-30, 37, and 48 are rejected under 35 U.S.C. 102(a) as being anticipated by Klein et al. (3/12/99) Blood, Vol. 94 (10), page 398A, abstract 1761. It is noted that Klein et al. represents a different inventive entity than that of the instant invention in that the authors C. Klein, G. Cheng, and R.C. Mulligan of the Klein et al. publication are not inventors of the instant invention. The applicant claims a composition of dendritic cells genetically modified to express a selectin polypeptide comprising an endothelial selectin ligand binding portion of a selection selected from a group which includes consists of L-selectin, E-selectin, and P-selectin, a vaccine comprising said cells and an antigen, methods of vaccinating comprising administering said vaccine, and methods of directing dendritic cells to secondary lymph nodes in vivo comprising administering said genetically modified dendritic cells.

Klein et al. teaches transduced dendritic cells which express the tumor antigen MAGE-1 and which express a chimeric E/L-selectin. Klein et al. further teaches that the administration of these transduced dendritic cells in vivo in mice results in the accumulation of the transduced dendritic cells in peripheral lymph nodes and the increased long-term survival of mice with pre-existing B16 MAGE 1 tumors. Thus, by teaching all the limitations of the claims, Klein et al. anticipates the instant invention.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 10:00-7:30. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

Dr. A.M.S. Beckerleg

A.M.S. BECKERLEG,
PATENT EXAMINER